IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

PERNIX IRELAND PAIN DAC and PERNIX THERAPEUTICS, LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 16-139-WCB
ALVOGEN MALTA OPERATIONS LTD.,	)	
Defendant.	)	

REPLY BRIEF IN SUPPORT OF ALVOGEN'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY UNDER 35 U.S.C. § 101

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I. INTRODUCTION

Alvogen's Section 101 Motion is based on a simple and narrow rule of law. Method of treatment claims that focus upon a natural law and rely upon that natural law as their sole inventive concept are invalid under 35 U.S.C. § 101 as patent-ineligible.

Seeking to avoid this rule, Pernix's Opposition is a study in misdirection. Pernix fails to explain why the rule is incorrect, choosing instead to quote out of context snippets from dicta in various cases that never address the question directly. Further, Pernix does not meaningfully dispute the underlying facts that establish application of the rule to the case at bar. Pernix ignores critical facts under the "directed to" inquiry of Step One and not once disputes that claim limitations outside the natural law itself are unconventional under Step Two.

In its Step One analysis, Pernix does not dispute the key facts demonstrating that the Asserted Claims are "directed to" a natural law. First, Pernix never disputes that all of its Asserted Claims do, in fact, recite a natural law, i.e., pharmacokinetic ("PK") profiles and non-adjustment of the starting dose. Second, Pernix never disputes that this natural law is the "basic concept" of the alleged invention and the reason the Patent Office allowed the Asserted Claims. In other words, the natural law represents the "focus" and "alleged advance" of the claimed subject matter, and the Asserted Claims are "directed to" it. Try as it might, Pernix cannot dodge this analysis through its request that this Court endorse an unprecedented *per se* rule of law holding all method of treatment claims patent eligible under Step One. Not only does the Supreme Court's holding in Mayo belie Pernix's position, but Pernix fails to cite to a single case showing that such a *per se* rule exists.

Pernix's Step Two analysis is equally flawed. Here, Pernix impermissibly relies on the natural law itself to demonstrate the allegedly unconventional nature of the Asserted Claims. Pernix, as it must, ignores binding Federal Circuit precedent holding that the inventive concept

cannot be furnished by the law of nature itself. Importantly, Pernix does not dispute that all remaining limitations of the Asserted Claims are conventional. Regardless, the PK and non-adjustment limitations reciting the natural law are indisputably conventional in any event. The PK limitations are directly analogous to, but even more conventional than the limitations reciting the natural law in Mayo. And Pernix does not meaningfully argue otherwise. The non-adjustment limitation is nothing more than the conventional result of following explicit testing and dosing instructions provided by FDA years before the filing of the Patents-In-Suit. Pernix's misguided attempt to apply the "law of the case" doctrine does nothing to change that fact.

In the end, Pernix cannot escape or dispute that the Asserted Claims are "directed to" a natural law and are otherwise conventional.

II. THE CLAIMS ARE DIRECTED TO A NATURAL LAW

The Asserted Claims are "directed to" a natural law because that is their "focus" and alleged "advance over the prior art." Enfish, LLC v. Microsoft Corp., 822 F.3d 1327, 1335 (Fed. Cir. 2016). Pernix ignores Alvogen's factual evidence and offers no explanation concerning why the Asserted Claims are "directed to" methods of treatment and a man-made substance under the governing legal standard. Instead, Pernix asks this Court to create a *per se* rule holding all method of treatment claims patent-eligible under Step One. No court has ever directly addressed this question, and the best Pernix can manage is to rely on piecemeal dicta in other cases.

A. The Natural Law Is The Focus Of The Asserted Claims.

Pernix's Opposition ignores critical intrinsic evidence from the Patents-In-Suit – evidence establishing that the Asserted Claims are "directed to" a natural law. First, Pernix summarily dismisses the specifications of the Patents-In-Suit, which characterize the natural law as the "basic concept" of the alleged inventions. (D.I. 139 at 9.) In so doing, Pernix mistakenly criticizes Alvogen for attempting to distill the Asserted Claims down to their basic concept. (Id.)

Alvogen did so because that is how binding Federal Circuit precedent defines the "directed to" inquiry. See, e.g., Genetic Techs. Ltd. v. Merial L.L.C., 818 F.3d 1369, 1375 (Fed. Cir. 2016). (inquiring into "the focus of the claimed advance over the prior art"). Indeed, Pernix's own Opposition acknowledges that Step One requires analyzing the "focus" of the claims. (D.I. 139 at 5 (citing McRO, Inc. v. Bandai Namco Games Am., Inc., 837 F.3d 1299 (Fed. Cir. 2016)).) Second, and along the same lines, Pernix improperly ignores the Patent Office's Reasons for Allowance, which characterize the natural law as the alleged advance relative to the prior art. (Ex. 8, PERNIX_HEP0000137.)

Shifting away from the proper standard, Pernix accuses Alvogen of ignoring the language of the claims. (D.I. 139 at 9.) Pernix fails to cite legal precedent holding the "language of the claims" controls the "directed to" inquiry. (Id.) Pernix further fails to explain how or why this inquiry elevates a known method of treatment and a copied prior art hydrocodone dosage form over the natural law that serves as the linchpin of its alleged invention. (Id.) In this way, Pernix creates a rudderless "directed to" standard that would permit reviewing courts to arbitrarily select any claim language they choose in order to hold that subject claims pass or fail Mayo Step One.

B. Method Of Treatment Claims Are Not *Per Se* Eligible Under Step One.

Notwithstanding its request for this Court to establish a brand new rule of law holding method of treatment claims *per se* patent eligible under Step One, Pernix fails to reconcile its position with the ultimate holding in Mayo. The dicta from the cases Pernix relies upon comes nowhere near establishing the broad rule it proposes. Perhaps more importantly, Pernix fails to cite even a single case actually holding that such a *per se* rule exists, and there is none.

Mayo itself demonstrates that method of treatment claims are "directed to" ineligible subject matter under Step One when they "focus" upon a natural law. The Mayo claims were "directed to" a natural law notwithstanding that they recited a method of treatment: "***A method***

of optimizing therapeutic efficacy ***for treatment of*** an immune-mediated gastrointestinal disorder." Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 74 (2012) (emphasis added). Further, Pernix fails to distinguish the ineligible method of treatment claims in Endo Pharms. Inc. v. Actavis Inc., No. 14-1381-RGA, 2015 WL 7253674 (D. Del. Nov. 17, 2015). A full reading of Endo demonstrates that the Court did not rely on the patentee's concession of Step One, but rather considered the specification of the patent-in-suit to conclude that the claims were "directed to" a natural law. Id. at *3. Pernix's further contention that Endo is distinguishable because it "left the treatment decision unresolved, instructing the physicians to . . . administer an unspecified 'lower dosage'" is also wrong. (D.I. 139 at 10.) Both the Endo claims and the Asserted Claims recite adjusted dosage amounts in relative unspecified terms. (See, e.g., D.I. 139 at 11 n.7; Ex. 1, '760 patent at claim 1.) Given the foregoing, Alvogen comes nowhere near invalidating *all* method of treatment claims, as Pernix erroneously contends.

The Federal Circuit's recent split-decision in Vanda also does not save Pernix under Step One. See Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd., No. 16-2707, -2708, 2018 WL 1770273, at *12-15 (Fed. Cir. Apr. 13, 2018) ("Vanda I"). There, the named inventors discovered that a specific dosing regimen of iloperidone may be employed to safely treat schizophrenia for the first time. Id. at *2; Vanda Pharms. Inc. v. Roxane Labs., Inc., 203 F. Supp. 3d 412, 427 (D. Del. 2016) ("Vanda II"). In fact, the original owner of iloperidone sold the compound and bought it back at a 40x valuation based on discovery of the dosing regimen. Vanda II, 203 F. Supp. 3d at 427. The Federal Circuit Majority thus held the claims were not "directed to" a natural law but rather treating schizophrenia by "administering" iloperidone in the specific dosing regimen – "internally administering iloperidone to the patient in an amount that is 12mg/day or less" or between "12mg/day" and "24mg/day." Vanda I, 2018 WL 1770273 at *14.

In contrast, the Asserted Claims here are analogous to Mayo. With respect to the Asserted Claims that recite PK values and no dosing regimen, Mayo controls and Vanda is inapposite. With respect to Asserted Claims reciting non-adjustment of starting dose, the prior art already taught safely administering hydrocodone dosage forms to treat pain in hepatic impairment ("HI") patients and administering is thus not the "focus" of the Asserted Claims. (See, e.g., Ex. 3, Johnson at ACT-HYD2-021171; Ex. 4, Smith at PERNIX_HEP0001545; Ex. 5, Jain at ¶ 64.) Such an "administering" step was also not the focus in Mayo.[1] Moreover, the administering step is even less relevant here, as Pernix contends that the non-adjustment limitation is complete prior to performing this step. (D.I. 120 at 12-13.) Finally, like Mayo and unlike Vanda, the Asserted Claims do not prescribe a specific dosing regimen, but rather a starting dose with subsequent dosing open to doctor and patient discretion.

In light of Mayo, Endo and Vanda, Pernix's overly broad *per se* rule improperly exempts all method of treatment claims in the biopharmaceutical field from patent ineligibility, no matter how prominent the role of a natural law is in those claims. Indeed, under the regime Pernix posits, patent applicants could simply disguise new discoveries of natural laws by drafting claims to include method of treatment preambles and automatically avoid patent ineligibility. But as the Supreme Court explained, patentable subject matter should not "depend simply on the draftsman's art." Parker v. Flook, 437 U.S. 584, 593 (1978).

Further, and as discussed in detail in Alvogen's Opposition to Pernix's Section 101 Motion, the dicta Pernix cites from the Supreme Court and Federal Circuit fails to support the proposition it advances. (D.I. 145 at 7-9.) Pernix takes the Mayo dicta out of context, arguing

[1] Chief Judge Prost, writing in dissent, found that the Majority's "efforts to distinguish Mayo cannot withstand scrutiny" and held the Vanda claims failed Steps One and Two. Vanda I, 2018 WL 1770273 at *18-21.

that any "new way of using an existing drug" passes Step One as a matter of law. (D.I. 139 at 6-7 (quoting Mayo, 566 U.S. at 87).) In fact, the passage Pernix quotes addresses Step Two and preemption, which is why the ultimate holding in Mayo conflicts with Pernix's position. With respect to CellzDirect, the dicta merely suggests that new methods of treatment are not "directed to" a natural law in all cases. (Id. at 7-8.)

Nor do the Patent Guidelines support Pernix's *per se* rule. Even if the Guidelines were controlling law (they are not), they are consistent with Mayo and Endo. Example Claim 7 in the Guidelines recites a method of treatment comprising administering anti-TNF antibodies to a patient with julitis. (D.I. 117-1 at 132.) The Guidelines state that claim 7 passed Step One because it was "directed to" the administering step, which does not qualify as a natural law. In other words, the "focus" of claim 7 was the administering step as opposed to a natural law in the form of the body's physiological response to TNF antibodies in patients with julitis. Here, in contrast, the focus of the Asserted Claims under the "directed to" standard is a natural law, not an administering step. (See supra at Section II(A).)

Finally, the Asserted Claims do not, as a matter of fact, cover "'a new way of using an existing drug'" or a "'new and improved way' of treating pain." (D.I. 139 at 6-7, 9.) The prior art already taught treating pain with hydrocodone extended-release ("HC-ER") dosage forms in patients with mild or moderate HI and that is exactly what the Asserted Claims cover. (Ex. 5, Jain at ¶ 64; Ex. 6, Devane at ¶¶ 70, 99-101, claim 81.) As such, it is not the case that the named inventors were first to conceive of using hydrocodone to effectively treat pain. Prior art HC-ER dosage forms effectively treated pain and continue to do so in the same way and with the same effect when doctors and patients practice the claimed methods. (Ex. 5, Jain at ¶ 64.)

III. THE ASSERTED CLAIMS ARE CONVENTIONAL

There can be no dispute of fact. Aside from Pernix's natural law itself, all limitations

recited by the Asserted Claims are conventional. Rather than address this problem head-on, Pernix ignores Federal Circuit precedent holding that the natural law itself is irrelevant to Step Two. But even if Pernix's law of nature were somehow relevant, it is in fact conventional. Pernix does not even attempt to explain how or why the PK limitations are unconventional. And close examination of the non-adjustment limitation supports the same conclusion.

A. Pernix Cannot Rely Upon The Law Of Nature Itself.

The law is clear. The "inventive concept necessary at step two cannot be furnished by the unpatentable law of nature [] itself." Genetic Techs., 818 F.3d at 1376. Nowhere in its Opposition does Pernix contest or disagree with this rule of law. And nowhere in its Opposition does Pernix assert that limitations outside its claimed natural law are unconventional. Instead, Pernix focuses almost exclusively on non-adjustment of the starting dose, which simply restates its natural law. Although Pernix also characterizes its "administering" step as unconventional, here too it relies upon non-adjustment of the starting dose to justify its position: "the claims here recite unconventional steps, namely, administering an ER hydrocodone oral dosage unit . . . **without adjusting the starting dose**." (D.I. 139 at 13 (emphasis added).) As Pernix itself admitted to this Court, all limitations recited by the Asserted Claims, outside the non-adjustment limitation, represent "mere empty language." (D.I. 65 at 4-5.) Regardless, Pernix's natural law itself, as recited by the Asserted Claims, is conventional.

B. The PK Limitations Are Conventional

Claims 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent are indisputably conventional because they recite nothing more than inherent PK values. These claims are analogous to, but even more conventional than the patent-ineligible claims in Mayo. Pernix does not even explain why the PK limitations are unconventional.

In Mayo, the claims at issue recited a method of treatment comprising administering a

thiopurine drug, along with an observation based on the human body's response to that drug, i.e., indicating a need to adjust the dose up or down. Mayo, 566 U.S. at 74-75. Claims 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent are directly analogous. They recite a method of treatment comprising administering hydrocodone with the same type of observation. In particular, the PK limitations are observations of the AUC and C_{max} in patients with and without HI, along with a comparison of the percent differences between the two or a specific AUC range. (Ex. 1, '760 patent at claims 12, 17 and 19; Ex. 2, '499 patent at claim 1.)

These limitations are more conventional and accomplish even less than those of Mayo. Whereas the Mayo limitations recited that the measured blood levels indicated a need to adjust the dosage, the PK limitations merely report inherent blood levels of the active drug without telling doctors or patients to do anything. It also bears noting that FDA mandated the observation here, i.e., a comparison of AUC and C_{max} values in HI patients for drugs metabolized by the liver. (Ex. 7, 2003 FDA Guidance at ACT-HYD-023065-068.)

Given the foregoing, Pernix only nominally addresses claims 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent. (D.I. 139 at 13.) Pernix incorrectly (and without support or explanation) contends that PK limitations "enabling" non-adjustment of starting doses transform a law of nature into a patent-eligible application of this law. The obvious flaw in Pernix's position is that it relies on a feature that is not included in the PK claims—non-adjustment—to contend that the PK claims include a non-conventional inventive concept. Pernix cannot re-write its claims to avoid patent ineligibility. The PK limitations represent a conventional observation. These claims fail Step Two as a matter of law.

C. The Non-adjustment Limitation Is Also Conventional

The natural law reciting non-adjustment of the starting dose, as recited by claims 1-4 and 11 of the '760 patent, is also indisputably conventional. This limitation reflects the teachings of

the 2003 FDA Guidance. Pernix cannot avoid the issue through the "law of the case" doctrine.

Non-adjustment of the starting dose in patients with mild or moderate HI is conventional because the 2003 FDA Guidance explains exactly when it is appropriate, and the prior art repeatedly teaches it. The FDA Guidance "recommends a PK study in patients with impaired hepatic function if hepatic metabolism and/or excretion accounts for a substantial portion (>20 percent of the absorbed drug) of the elimination of a parent drug or active metabolite." (Ex. 7, 2003 FDA Guidance at ACT-HYD2-023063.) The Guidance further specifies that dose adjustment in such HI patients is necessary when "the effect of hepatic impairment on the PK of the drug is obvious (e.g., two-fold or greater increase in AUC). . . ." (Id. at ACT-HYD-023067.) It is simply not inventive to observe standard AUC and C_{max} measurements in patients with and without HI, as required by an FDA Guidance, and then adhere to dosing instructions provided by that Guidance. (Schmidt Decl. Ex. A at ¶¶ 132-134.) The Asserted Claims simply direct doctors to apply the natural law in a routine and conventional manner. See Mayo, 566 U.S. at 72 (one must do more than add the words "apply it" to a natural law.)

Indeed, the named inventors were certainly not the first to follow the natural law that non-adjustment of starting doses for certain opioids was appropriate in HI patients. The label for the opioid tapentadol ER (Nucynta®) states that "[n]o dosage adjustment is recommended in patients with mild hepatic impairment." (Ex. 9, Nucynta® ER Label at ACT-HYD2-023370. See also Ex. 10, Exalgo™ Label at PERNIX_HEP0013311.) Moreover, in seeking FDA approval for Zohydro® ER, Zogenix relied on the hydrocodone dosage forms Vicodin® and Vicoprofen® as reference drugs, neither of which required a dose adjustment in patients with mild or moderate HI. (Ex. 11, Hartman Dep. Tr. at 96:3-99:6; Ex. 12, Vicodin® Label at ACT-HYD2-022214; Ex. 13, Vicoprofen® Label at ACT-HYD2-023201.) That several prior art

references teach adjustment of opioid starting doses in patients with HI makes Pernix's non-adjustment no less prevalent or conventional.

Pernix thus retreats to and repeats its unprecedented argument that a footnote in the Court's Markman Order precludes Alvogen from asserting that the non-adjustment limitation is conventional under the "law of the case" doctrine. (D.I. 139 at 13-14.) As discussed at length in Alvogen's Opposition (D.I. 145 at 20-23,) Pernix is wrong as a matter of law and fact. (Id.)

IV. PREEMPTION IS PRESENT

The Asserted Claims preempt use of the natural law covering the comparable bioavailability of hydrocodone in the body of patients with and without mild or moderate HI after administration of certain HC-ER formulations. Pernix's assertion that "no such law exists" misconstrues Alvogen's preemption analysis. (D.I. 139 at 16.) Alvogen's primary point was and is that the Asserted Claims unfairly monopolize or preempt administration of any HC-ER dosage form that satisfies the natural law. (D.I. 112 at 15.) Put another way, and as set forth in Alvogen's Section 101 Motion and Opposition, preemption applies to only certain hydrocodone formulations, not all hydrocodone formulations under the sun. (D.I. 112 at 15; D.I. 145 at 24.) For these reasons, the hydrocodone oral dosage form in the Bond abstract, later approved as Vantrela™ ER, is irrelevant to preemption. By Pernix's own admission, Vantrela™ ER is irrelevant because the key question is whether the Asserted Claims preempt hydrocodone formulations that satisfy the non-adjustment and PK wherein clauses and this dosage form does not. (D.I. 139 at 16).

V. CONCLUSION

For the foregoing reasons, Alvogen requests that the Court enter summary judgment in Alvogen's favor that the Asserted Claims are invalid under § 101.

Respectfully submitted,

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